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# The burden and costs of sepsis and reimbursement of its treatment in a developing country: An observational study on focal infections in Indonesia

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ABSTRACT

*Objectives:* This study aimed to determine the burden of sepsis with focal infections in the resource-limited context of Indonesia and to propose national prices for sepsis reimbursement.
*Methods:* A retrospective observational study was conducted from 2013–2016 on cost of surviving and non-surviving sepsis patients from a payer perspective using inpatient billing records in four hospitals. The national burden of sepsis was calculated and proposed national prices for reimbursement were developed.
*Results:* Of the 14,076 sepsis patients, 5,876 (41.7%) survived and 8,200 (58.3%) died. The mean hospital costs incurred per surviving and deceased sepsis patient were US$1,011 (SE ± 23.4) and US$1,406 (SE ± 27.8), respectively. The national burden of sepsis in 100,000 patients was estimated to be US$130 million. Sepsis patients with multifocal infections and a single focal lower-respiratory tract infection (LRTI) were estimated as being the two with the highest economic burden (US$48 million and US$33 million, respectively, within 100,000 sepsis patients). Sepsis with cardiovascular infection was estimated to warrant the highest proposed national price for reimbursement (US$4,256).
*Conclusions:* Multifocal infections and LRTIs are the major focal infections with the highest burden of sepsis. This study showed varying cost estimates for sepsis, necessitating a new reimbursement system with adjustment of the national prices taking the particular foci into account.


## Introduction

Sepsis is estimated to involve 31.5 million cases each year worldwide (Fleischmann et al. 2016). Of these cases, 19.4 million are characterized by severe sepsis, accounting for 5.3 million deaths annually (Fleischmann et al. 2016). These estimates are derived from data compiled for high-income countries. However, the highest

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mortalities occur in low-income countries, followed by low-middle income countries (LMICs) (Cheng et al. 2008). There is a surprising lack of data on mortality and costs among sepsis patients in LMICs such as most African and Asian countries, including Indonesia (Fleischmann et al. 2016; Rudd et al. 2018). Indonesia, which is the most populated country in Southeast Asia and the fourth most populated country globally, has a high incidence of communicable diseases (Gupta and Guin 2010; The world bank 2018). Ascertaining the granularity of the sepsis burden in Indonesia has become essential in light of the government's introduction of a new national health insurance system (Jaminan Kesehatan Nasional) (Health Ministry of the Republic of Indonesia 2014). In 2018, universal health coverage (UHC), provided by a single national payer, became available for 203 million people (Agustina et al. 2019). During the period 2019–2020, coverage will be extended to the entire Indonesian population (approximately 264 million people) (The world bank 2018; Agustina et al. 2019). Accordingly, a national reimbursement price for each disease will need to be accounted for within the reimbursement system (Pisani et al. 2017; Mboi et al. 2018; Agustina et al. 2019).

The economic burden of sepsis, which includes providing medication and fluid resuscitation during hospitalization, has been reported to be very high (McLaughlin et al. 2009). In the United States, hospitalization costs for sepsis patients were approximately US$20 billion in 2011 (Pfuntner et al. 2006). A previous systematic review, which mostly included studies performed in the United States, revealed that an essential analysis of the economic burden of sepsis concerned an evaluation between survivors and non-survivors because of a major difference in the mean total hospital costs per day (US$351 vs. US$948, respectively) (Arefian et al. 2017). The difference in burden between survivors and non-survivors is unknown in LMICs. International budgetary guidelines for sepsis management mostly apply to developed countries and therefore may require cost adjustments of service bundles relating to sepsis management in resource-limited settings (Becker et al. 2009; Tufan et al. 2015).

A focal infection terminology was firstly introduced in 1910 by William Hunter, who elaborated the relationship between focal infections and systemic diseases (Reimann and Havens 1940). A focal infection is a potential source of microorganisms that may disseminate into deep tissue and spread to the bloodstream. A further impact of the dissemination of the microorganisms and their toxin in the bloodstream is activation of the inflammatory mediators and worsening organ dysfunction due to sepsis (Babu and Gomes 2011). According to the third consensus definitions for sepsis and septic shock (Singer et al. 2016), sepsis has at least an underlying focal infection as an entry of the pathogen to the systemic circulation. Each focal infection causing sepsis comes with different complications, with a wide range of costs. Therefore, the reimbursement of sepsis needs cost adjustments according to the underlying focal infection. In Indonesia, sepsis and the associated focal infections are not coded together when calculating the national price of diseases, resulting in possible under-budgeting for sepsis-related expenditure (Health Ministry of the Republic of Indonesia, 2016). Therefore, a reevaluation of the costs for sepsis has become urgent for countries like Indonesia, including dealing with underlying focal infections. This study analyzed costs for surviving and deceased sepsis patients, explicitly considering underlying focal infections. In addition, it then estimated national prices for reimbursement under UHC based on the analyzed burden and costs of sepsis.

## Methods

### *Study design*

A retrospective observational study was conducted on patients with sepsis in four Indonesian medical centers: (1) Dr. Soetomo General Academic Hospital in Surabaya, a national healthcare referral center, with 1,514 beds, serving eastern Indonesia; (2) Universitas Airlangga Hospital in Surabaya, a teaching medical center with 180 beds in Surabaya; (3) The Prof. Dr. Sulianti Saroso National Center for Infectious Diseases Hospital, with 180 beds in Jakarta; and (4) Dr. M. Djamil Hospital in Padang, a national referral center with 800 beds, serving western Indonesia. Inpatient registries and hospital discharge data were obtained from the Department of Medical Records for the period 01 January 2013 to 31 December 2016. The dataset covered patients' demographics, diagnoses, hospital-discharge mortalities, laboratory tests, and medications.

### *Criteria for selecting patients*

All patients with sepsis and aged $\geq$ 18 years were included. The diagnosis of sepsis was clarified by the physicians. The criteria for sepsis diagnosis followed the Indonesian Ministry of Health adopted Third International Consensus Definitions for Sepsis and Shock, Sepsis-3 (Singer et al. 2016) and diagnostic criteria for sepsis entailed in the Sequential Organ Failure Assessment (SOFA) score that includes at least two of the following three 'quick' SOFA (qSOFA) criteria: systolic blood pressure $\leq$ 100 mmHg, respiratory rate $\geq$ 22 breaths per minute, and incorporating altered mentation (Glasgow Coma Scale score < 15) (Health Ministry of the Republic of Indonesia 2017). The study categorized single focal infections per site of the infection as cardiovascular infections (CVIs), gastrointestinal tract infections (GTIs), lower-respiratory tract infections (LRTIs), neuromuscular infections (NMIs), urinary tract infections (UTIs), and wound infections (WIs). WIs recognized at the sites of surgery were subclassified as surgical site infections (SSIs). The physicians confirmed SSI diagnoses according to the Centers for Diseases Control and Prevention (Horan et al. 1992). Focal mouth and dental infections were included in the NMI category since those infections anatomically involved soft tissues such as nerves and muscles. Sepsis patients with two or more focal infections were grouped into sepsis with multifocal infections. Moreover, an unspecified focal infection was labeled as an unidentified focal infection (UFI). The International Classification of Diseases version 10 was applied to determine and record focal infections (see Supplement 1).

### *Cost calculation*

Cost was analyzed from a payer perspective using billing records that included the costs of beds, drugs, laboratory and radiology procedures, other medical facilities, and total costs. Bed costs encompassed hospital administration fees, daily room services, nursing and medical staff care, and technicians' services. Drug costs were extracted from the pharmacy department's budget that covered expenses relating to drugs, fluids, blood products for transfusion, disposable devices, mechanical ventilators, oxygen therapy, and pharmacy services. Physiotherapists' – as rehabilitation specialists – consultancy costs were recorded and considered under patients' bed service costs. Costs for administrations, patient transfer and ambulance, and other expenses were included in the costs for other medical facilities. The hospitalization costs per admission were analyzed, considering the days spent in an intensive care unit (ICU), presence of SSIs, types of focal infections, and whether the patient survived or not. The 2016 currency exchange rate (US$1 = 13,308.33 IDR) was used, as applied by the Organization for Economic Cooperation and Development (OECD) to convert Indonesian Rupiahs (IDR) into US Dollars (US$) (Organization for Economic Cooperation and Development 2016), with inflation rates of 6.40% for 2013, 6.42% for 2014, 6.38% for 2015, and 3.53% for 2016 (Worldwide Inflation

Data 2020). The economic burden of sepsis was assessed according to the distribution of disease incidence over focal infections and the mean cost of each focal infection using a denominator of 100,000 patients with sepsis (The World Bank 2016a).

*Extrapolation of the cost to the national level*

The national costs for sepsis were analyzed based on the rates defined by the Indonesian Health Ministry for Indonesia Case Base Groups (INA-CBGs). The INA-CBGs' rates were used as national projections for extrapolating the sepsis costs – obtained from patient's billing records – into Proposed National Prices (PNPs) for sepsis reimbursements by considering the following four aspects (Health Ministry of the Republic of Indonesia, 2016).

The first aspect concerned the room classes in the hospital, which were divided into three classes: Class I, patients had more privacy within one room, accommodating up to two patients; Class II accommodating three or four people; Class III service accommodating five or six people in a room (Health Ministry of the Republic of Indonesia, 2016; President of Republic of Indonesia 2016). This study provided the PNP in Class III as the reference. It calculated the actual costs from Classes I, II and III ($\overline{CP}$) – obtained from patient's billing records – and divided them by the specific factor ($\alpha$) according to the INA-CBGs at 1.4, 1.2, and 1.0, respectively (Health Ministry of the Republic of Indonesia, 2016).

The second aspect concerned private or public sector ownership of the hospital. In the INA-CBG system, reimbursement provided by the government through subsidies was 1.03 ($\beta$) times higher for private healthcare services compared with the public healthcare services (Health Ministry of the Republic of Indonesia, 2016).

The third and fourth aspects concerned the type of hospital and the region where the hospital is located, to correspond with the specific INA-CBG prices (ICPj) that were published by the Indonesian Ministry of Health in 2016 (Health Ministry of the Republic of Indonesia, 2016). The classification of hospital type in Indonesia was categorized into types A, B, C and D on the basis of the medical specialist services (see Supplement 2) (Health Ministry of the Republic of Indonesia, 2016; President of Republic of Indonesia 2016; Health Ministry of the Republic of Indonesia, 2019). There were five INA-CBG regions covering 34 provinces in total (Supplement 3) (Health Ministry of the Republic of Indonesia, 2016). The ICP for hospital type A in Region I was used as the denominator reference for ICP in the calculation of a PNP, since the actual costs were obtained from the hospitals with type A located in the INA-CBG Region I. Eventually, for a particular focal infection inpatient, in a class of room, in a specific type of hospital, in a certain region under the private or the public sectors, a PNP for sepsis with an x focal infection was defined as in the following formula:

$$PNP_x = \left[\left(\frac{\overline{CP}}{\alpha}\right)\left(\frac{ICP_j}{ICP_{Hospital\ Type\ A\ in\ Region\ I}}\right)\right]\beta$$

In brief, the four aspects for developing a PNP were the mean actual costs reflecting the single mean class price ($\overline{CP}$), the specific factor ($\alpha$) of each Class room, the specific INA-CBG prices (ICPj), and the government subsidy factor ($\beta$). This study developed 280 PNPs (seven focal infections, four types of hospitals, two sectors, and five regions) for reimbursement of sepsis with particular focal infections in the five INA-CBG regions. To compare with the reference ICPs, the PNPs were categorized into three groups: those with a small difference with the ICP of < US$500, a medium difference of US$500–1,000, and a major difference > US$1,000.

*Statistical analyses*

Data were analyzed using IBM SPSS statistics 25, providing descriptive data on baseline characteristics in percentages. Chi-square tests were performed to determine the differences between surviving and deceased sepsis patients. 1,000 samples were bootstrapped, and in cases where the data were overly skewed the standard error (SE) was adjusted for the mean cost. An Independent Sample t-test was applied to evaluate the statistical cost difference between the surviving and deceased patient groups. Subgroup analyses of hospitalization costs relating to ICU treatment, having SSIs, and types of focal infections were performed. Statistical significance was defined when the $p$-value was < 0.05.

## Results

Of the 14,076 patients with sepsis, 5,876 (41.7%) survived and 8,200 (58.3%) died. The patients were predominantly male (53%). The average age among all patients was 49.4 (± 18.9) years. Surviving and deceased sepsis patients evidenced statistical differences for the following single focal infections: LRTIs (38% vs. 62%, respectively, $p < 0.001$), UTIs (56% vs. 44%, respectively, $p < 0.001$), and WIs (18% vs. 82%, respectively, $p < 0.001$). Thirty-one percent of the sepsis patients were diagnosed with multifocal infections with a significant difference between surviving and deceased patients (40% vs. 60%, respectively, $p < 0.001$). Of the 2,138 sepsis patients with SSIs, 74.2% died. Also, patients with sepsis who were hospitalized in an ICU demonstrated a high case fatality rate (69%). Table 1 presents a summary of the clinical characteristics of surviving and deceased sepsis patients.

*Hospitalization costs*

The costs per admission for surviving and deceased sepsis patients were, respectively: US$1,011 (± 23.4) and US$1,406 (± 27.8) (i.e., a difference of US$396, $p < 0.001$). The mean cost for all sepsis cases was US$1,253 (± 19.4). Among non-ICU sepsis patients, the average cost was lower for surviving patients (US $960 ± 24.3) compared with that of deceased patients (US$1,189 ± 23.6) per admission ($p < 0.001$). For ICU sepsis patients, the cost per admission was US$1,618 (± 47.9), with respective mean costs of US $1,187 (± 61.7) and US$1,785.5 (± 56.3) for surviving and deceased patients ($p < 0.001$), respectively. The cost incurred for patients with sepsis who had SSIs was higher compared with that incurred for patients who did not have SSIs (US$2,938 vs. US$926). Table 2 shows these costs divided into unit costs for beds, laboratory and radiology, pharmacy, and other medical facilities.

*The national burden of sepsis*

The analyses of the treatment costs per admission for sepsis patients with focal infections (see Table 2) indicated that the cost was highest for sepsis patients with CVIs (US$1,731), followed by those with WIs (US$1,703), multifocal infections (US$1,584), LRTIs (US$1,122), NMIs (US$986), UTIs (US$748), and GTIs (US$720). The national burden of sepsis revealed a total budget of US$130 million (± US$5,7 million) per 100,000 patients. Sepsis with multifocal infections had the highest national burden of disease within 100,000 sepsis patients (US$48 million), followed by sepsis with LRTIs (US$33 million), UFIs (US$15 million), UTIs (US$11 million), GTIs (US$10.7 million), WIs (US$8.6 million), NMIs (US$2.7 million), and CVIs (US$0.9 million). Figure 1 depicts the economic burden of sepsis with focal infections.

**Table 1**
Baseline characteristics of surviving and deceased sepsis patients.

| Characteristics | All cases (n = 14,067) | % | Survivors (n = 5,876) | % | Deceased (n = 8,200) | % | *p*-value |
|---|---|---|---|---|---|---|---|
| Sex | | | | | | | |
| Male | 7,467 | 53.0 | 3,115 | 41.7 | 4,352 | 58.3 | 0.943 |
| Female | 6,609 | 47.0 | 2,761 | 41.8 | 3,848 | 58.2 | |
| Aged ≥ 60 years | 1,638 | 11.6 | 626 | 38.2 | 1,012 | 61.8 | 0.002 |
| Single focal infections | | | | | | | |
| CVI | 110 | 0.8 | 39 | 35.5 | 71 | 64.5 | 0.179 |
| GTI | 1,328 | 9.4 | 565 | 42.5 | 763 | 57.5 | 0.534 |
| LRTI | 3,932 | 27.9 | 1,486 | 37.8 | 2,446 | 62.2 | < 0.001* |
| NMI | 368 | 2.6 | 153 | 41.6 | 215 | 58.4 | 0.947 |
| UTI | 1,348 | 9.6 | 755 | 56.0 | 593 | 44.0 | < 0.001* |
| WI | 1,049 | 7.5 | 191 | 18.2 | 858 | 81.8 | < 0.001* |
| Multifocal infections | 4,304 | 30.6 | 1,700 | 39.5 | 2,604 | 60.5 | < 0.001* |
| UFI sepsis | 1,637 | 11.6 | 987 | 60.3 | 650 | 39.7 | < 0.001* |
| Having SSIs | 2,138 | 15.2 | 551 | 25.8 | 1,587 | 74.2 | < 0.001* |
| ICU | 4,297 | 30.8 | 1,328 | 30.9 | 2,969 | 69.1 | < 0.001* |

Abbreviations: CVI, cardiovascular infections; GTI, gastrointestinal tract infection; ICU, intensive care unit; LRTI, lower-respiratory tract infection; NMI, neuromuscular infection; SSI, surgical site infection; UFI, unidentified focal infection; UTI, urinary tract infection; WI, wound infection.
* Statistically significant, $p < 0.05$.

**Table 2**
Hospitalization costs for sepsis patients per admission (in 2016 US$).

| Hospitalization cost | All cases mean (SE) | Survived mean (SE) | Deceasedmean (SE) | Cost difference | *p*-value |
|---|---|---|---|---|---|
| **Non-ICU stay** | | | | | |
| Bed costs | 222.12 (3.72) | 196.31 (5.17) | 242.16 (4.95) | 45.85 (7.49) | < 0.001 |
| Laboratory and radiology costs | 327.29 (6.24) | 276.49 (8.65) | 366.49 (8.28) | 90.01 (12.55) | < 0.001 |
| Pharmacy costs | 404.61 (7.15) | 369.76 (10.37) | 431.74 (9.53) | 61.98 (14.40) | < 0.001 |
| Other medical facilities costs | 142.14 (2.30) | 126.49 (3.24) | 154.29 (3.07) | 27.80 (4.64) | < 0.001 |
| **ICU stay** | | | | | |
| Bed costs | 330.29 (9.81) | 243.08 (13.05) | 364.27 (11.52) | 121.19 (21.76) | < 0.001 |
| Laboratory and radiology costs | 416.60 (14.29) | 297.47 (18.40) | 462.711 (16.77) | 165.25 (31.74) | < 0.001 |
| Pharmacy costs | 662.612 (20.59) | 491.54 (26.36) | 729.47 (24.19) | 237.93 (45.64) | < 0.001 |
| Other medical facilities costs | 207.33 (6.07) | 151.53 (7.56) | 229.08 (7.12) | 77.56 (13.45) | < 0.001 |
| **Having SSIs** | | | | | |
| No | 925.92 (13.13) | 838.59 (19.75) | 988.55 (17.18) | 149.96 (26.58) | < 0.001* |
| Yes | 2,937.89 (88.80) | 2,595.84 (133.88) | 3,042.17 (101.32) | 446.33 (209.61) | 0.033* |
| **Types of focal infections** | | | | | |
| CVI | 1,731.09 (90.18) | 1,634.30 (168.91) | 1,750.87 (98.95) | 116.57 (240.24) | 0.628 |
| GTI | 719.76 (25.12) | 618.06 (33.50) | 792.711 (32.77) | 174.65 (50.70) | 0.001* |
| LRTI | 1,122.47 (29.76) | 818.83 (30.51) | 1,306.77 (37.42) | 487.94 (60.88) | < 0.001* |
| NMI | 985.62 (73.65) | 855.84 (101.65) | 1,076.29 (95.69) | 220.45 (149.21) | 0.140 |
| UTI | 747.83 (29.81) | 733.51 (41.95) | 765.31 (44.42) | 31.81 (59.91) | 0.595 |
| WI | 1,702.58 (221.88) | 1,579.36 (264.01) | 1,765 (272.84) | 186.60 (468.17) | 0.690 |
| Multifocal infections | 1,583.51 (19.36) | 1,363.16 (51.83) | 1,723.78 (56.05) | 395.64 (39.58) | < 0.001* |
| UFI | 1,268.26 (65.14) | 1,315.27 (84.09) | 1,197.25 (102.94) | 118.02 (133.11) | 0.375 |

Abbreviations: CVI, cardiovascular infections; GTI, gastrointestinal tract infection; ICU, intensive care unit; LRTI, lower-respiratory tract infection; NMI, neuromuscular infection; SSI, surgical site infection; SE, standard error; UFI, unidentified focal infection; UTI, urinary tract infection; WI, wound infection.
* Statistically significant, $p < 0.05$.

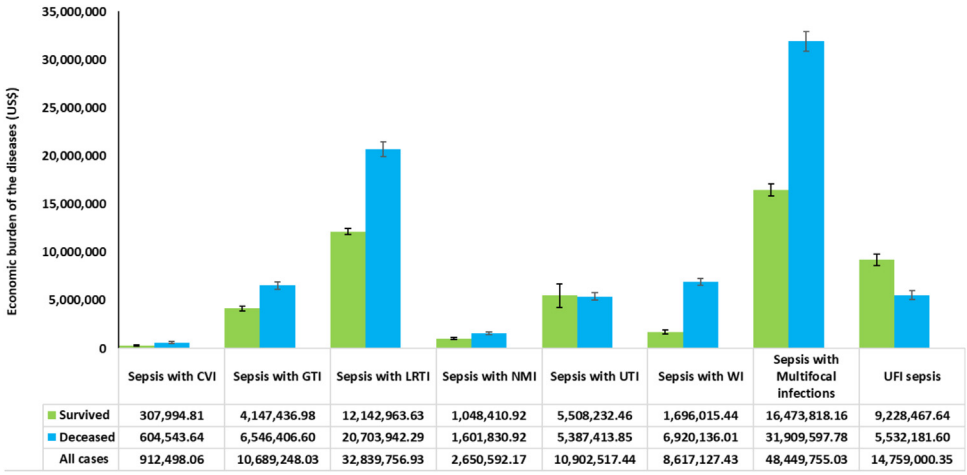
*The prospective national price for sepsis patients*

The lowest price within the INA-CBG system (ICP) was for UFI sepsis, with the ICP at US$298 in a type D public hospital in Region 1, for which a PNP of US$803 was estimated (difference: US$505). The highest PNP was for sepsis with CVIs in type A private hospitals in Region 5 (US$4,256) compared with the ICP of US$2,270 (difference: US$1,986). A remarkable difference between the PNP and ICP was evident for healthcare services relating to sepsis with WIs in type A private hospitals in Region 5 (US$3,995 vs. US$1,421; difference: US$2,574). Reimbursement levels under the overall PNP for sepsis were higher for all types of private hospitals compared with those for public hospitals (all types) in all INA-CBG regions. Out of 280 PNPs, 87 (31.1%) had major differences from the reference ICPs (> US$1,000). PNPs with a major difference were predominantly for reimbursement of sepsis with WIs (Table 3). Supplement 4 presents the details between the PNPs and the rates specified for the ICPs for sepsis with focal infections in all five regions of Indonesia.

## Discussion

In this study, the economic burden for focal infections associated with sepsis was comprehensively determined in the resource-limited setting in Indonesia. Sepsis was mostly induced by LRTIs, accounting for the high associated total cost per patient. Besides LRTIs, the findings indicated a strong correlation between high costs and having SSIs. The costs especially increased for patients with multifocal infections. In the broader scale, the economic burden of sepsis with focal infections was higher for deceased patients than for surviving patients. In the new Indonesian UHC system, the reimbursement for sepsis entails four aspects: class of patient's room, government subsidies, type of hospital, and INA-CBG region. Moreover, the current findings show the great difference in costs between PNP and ICP, especially for sepsis-related costs with the focal infections of WIs and CVIs.

There is convincing evidence of a positive correlation between LRTIs and sepsis with regard to mortality outcome (Jaja et al. 2019). Over the last decade, LRTIs have been the most prevalent




| | Sepsis with CVI | Sepsis with GTI | Sepsis with LRTI | Sepsis with NMI | Sepsis with UTI | Sepsis with WI | Sepsis with Multifocal infections | UFI sepsis |
|---|---|---|---|---|---|---|---|---|
| Survived | 307,994.81 | 4,147,436.98 | 12,142,963.63 | 1,048,410.92 | 5,508,232.46 | 1,696,015.44 | 16,473,818.16 | 9,228,467.64 |
| Deceased | 604,543.64 | 6,546,406.60 | 20,703,942.29 | 1,601,830.92 | 5,387,413.85 | 6,920,136.01 | 31,909,597.78 | 5,532,181.60 |
| All cases | 912,498.06 | 10,689,248.03 | 32,839,756.93 | 2,650,592.17 | 10,902,517.44 | 8,617,127.43 | 48,449,755.03 | 14,759,000.35 |

**Figure 1.** The economic burden of sepsis with particular focal infections for 100,000 patients with survived (in green) and deceased (in blue) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).
*Note:* CVI = cardiovascular infections, GTI = gastrointestinal tract infection, LRTI = lower-respiratory tract infection, NMI = neuromuscular infection, UFI = unidentified focal infection, UTI = urinary tract infection, and WI = wound infection.

communicable disease in Indonesia (2018). The economic burden of sepsis with LRTIs in ICUs in a developing country such as Turkey was estimated at US$2,722 per patient (Gumus et al. 2019). In addition, LRTIs such as community-acquired pneumonia contribute high morbidity in terms of more hospitalizations for ICU admissions, requiring mechanical ventilators, and further sepsis complications (Sligl and Marrie 2013; Remington and Sligl 2014; Montull et al. 2016). In addition, elevated hospitalization costs for ICU patients with LRTIs were strongly associated with the use of a mechanical ventilator, presence of severe sepsis and septic shock (Gumus et al. 2019). Confirming these results, some studies have reported that in addition to being induced by LRTIs, sepsis also originates from WIs, GTIs and UTIs (approximately 16.5%, 16.7% and 28.3%, respectively) (Mayr et al. 2014; Jaja et al. 2019; Shankar-Hari et al. 2019). Sepsis arising from GTIs and WIs is mostly associated with surgical wounds (Muresan et al. 2018; Jaja et al. 2019). Infections on the site of surgeries after elective and emergency procedures that contribute to sepsis account for 5.8% and 24.8%, respectively (Shankar-Hari et al. 2019). A previous study covering 6.5 million elective surgeries performed in the United States reported an incidence of 1.2% of post-surgical sepsis cases, with a high mortality rate of 26% (Vogel et al. 2010). The current data revealed a high case fatality rate of sepsis with SSI. SSI-related costs that include medicines, prolonged length of stay and readmission could rise to US$22,130 per patient (Purba et al. 2018).

In the current study, sepsis with CVIs presented the highest cost per inpatient but accounted for the lowest national economic burden for sepsis, with focal infections giving relatively low numbers. In a previous systematic review, endocarditis was reported to be a rare disease with costly consequences (Abegaz et al. 2017). Sepsis with UTIs, or urosepsis, commonly causes kidney dysfunction, leading to high mortality rates. In the current study, the urinary tract ranked third in incidence as an infection site associated with sepsis. The incidence of urosepsis in the United States is about 30% and is higher among women compared with men (Esper et al. 2006; Kumar et al. 2019). The study was in line with the current findings, where among UTIs the female and male ratio was at 2:1. The incidence of sepsis associated with multifocal infections remains unknown, particularly in developing countries, but it was found that they are the costliest. Identifying multisource infections with sepsis prior to the occurrence of organ dysfunction is thus an urgent task (Zhou et al. 2019).

The further impacts of sepsis-related costs should be considered when formulating a national budget to support private and public healthcare services. In 2016, Indonesia's health expenditure was approximately US$111.6 billion or 3.1% of its GDP (The World Bank 2016b). Thus, establishing sufficient healthcare facilities to support the care of sepsis patients is a challenge. According to the National Health Account data published by the OECD in 2016, Indonesia's inpatient expenditure amounted to IDR158,499.2 billion (or US$11.9 billion) (Organization for Economic Cooperation and Development 2016; The World Bank 2016b). This expenditure accounts for 40.9% of the country's national total health expenditure of IDR387,648.5 billion or US$29.1 billion (The World Bank 2016b). For the sepsis inpatient expenditure, the current findings suggest that the prices in the current INA-CBGs should be upwardly adjusted as well as made specific for infection sites. As a specific item in the INA-CBGs, each individual pays health coverage according to the class of service selected. The service class categories merely relate to the provision of rooms with specific numbers of beds. Therefore, this categorization is ineffective, as all patients receive the same medical services or even when they are placed in ICUs or isolated rooms. Additionally, community healthcare centers, which play an essential role in resource-limited settings in preventing infection complications such as sepsis, could potentially serve as a budget control mechanism by averting hospital infections and then reducing inpatient costs (Kumar et al. 2019).

It is believed that this is the first study to assess the burden of disease, incorporating the costs and mortality outcomes of sepsis with focal infections, in a resource-limited setting. Notably, it offers a robust methodology for calculating the national price for sepsis based on a consideration of particular focal infections. However, the study had several limitations. First, it did not assess the costs associated with losses in productivity during hospitalization, and indirect costs were not recorded. Moreover, infrastructure costs – such as security systems, parking and transportation – were not included. Second, post-sepsis impact on individual patients' occupational or educational trajectories, and those of their relatives, was not assessed because the data obtained from the hospitals were not linked to the socioeconomic statuses of individual patients. Third, the national price was modeled with reference to four referral centers. Nevertheless, the resulting national model seemed reasonable. Forth, it was a retrospective study and potential bias could have existed such as misdiagnosis

**Table 3**
The proposed national price per patient for sepsis with focal infections in all five regions of Indonesia (in 2016 US$).

| Regional | Hospital | Sepsis with GTI | Sepsis with NMI | Sepsis with UTI | UFI sepsis | Sepsis with LRTI | Sepsis with CVI | Sepsis with WI* |
|---|---|---|---|---|---|---|---|---|
| **Region 1** | Public A | 1,296.9 | 1,770.9 | 2,084.1 | 1,721.0 | 3,023.6 | 3,897.8 | 3,659.4 |
| | Private A | 1,335.9 | 1,824.1 | 2,146.7 | 1,772.6 | 3,114.3 | 4,014.7 | 3,769.2 |
| | Public B | 1,003.8 | 1,239.3 | 1,346.6 | 1,204.3 | 1,754.6 | 2,727.7 | 2,654.4 |
| | Private B | 1,033.9 | 1,276.5 | 1,329.9 | 1,240.5 | 1,807.2 | 2,668.6 | 2,734.0 |
| | Public C | 806.2 | 995.3 | 1,172.1 | 967.2 | 1,594.7 | 2,118.4 | 2,281.1 |
| | Private C | 830.3 | 1,025.2 | 1,207.2 | 996.2 | 1,642.6 | 2,181.9 | 2,349.6 |
| | Public D | 669.8 | 827.0 | 1,019.4 | 803.6 | 1,395.4 | 1,820.1 | 1,770.4 |
| | Private D | 689.9 | 851.8 | 1,050.0 | 827.7 | 1,437.2 | 1,874.7 | 1,823.5 |
| **Region 2** | Public A | 1,308.6 | 1,786.9 | 2,102.9 | 1,736.5 | 3,050.8 | 3,932.9 | 3,692.4 |
| | Private A | 1,347.9 | 1,840.5 | 2,166.0 | 1,788.5 | 3,142.3 | 4,050.9 | 3,803.2 |
| | Public B | 1,012.8 | 1,250.5 | 1,302.8 | 1,215.2 | 1,770.4 | 2,752.2 | 2,678.3 |
| | Private B | 1,043.2 | 1,288.0 | 1,341.9 | 1,251.6 | 1,823.5 | 2,834.8 | 2,758.6 |
| | Public C | 813.4 | 1,004.3 | 1,182.6 | 975.9 | 1,609.1 | 2,137.4 | 2,301.7 |
| | Private C | 837.8 | 1,034.4 | 1,218.1 | 1,005.2 | 1,657.3 | 2,201.6 | 2,370.7 |
| | Public D | 675.8 | 834.4 | 1,028.6 | 810.8 | 1,407.9 | 1,836.5 | 1,786.3 |
| | Private D | 696.1 | 859.4 | 1,059.4 | 835.2 | 1,450.2 | 1,891.6 | 1,839.9 |
| **Region 3** | Public A | 1,312.5 | 1,792.2 | 2,109.2 | 1,741.6 | 3,059.8 | 3,944.6 | 3,703.4 |
| | Private A | 1,351.9 | 1,846.0 | 2,172.4 | 1,793.9 | 3,151.6 | 4,062.9 | 3,814.5 |
| | Public B | 1,015.8 | 1,254.2 | 1,306.7 | 1,218.8 | 1,775.6 | 2,760.4 | 2,686.3 |
| | Private B | 1,046.3 | 1,291.8 | 1,345.9 | 1,255.3 | 1,828.9 | 2,843.3 | 2,766.9 |
| | Public C | 815.8 | 1,007.2 | 1,186.1 | 978.8 | 1,613.9 | 2,143.8 | 2,308.5 |
| | Private C | 840.3 | 1,037.4 | 1,221.7 | 1,008.2 | 1,662.3 | 2,208.1 | 2,377.8 |
| | Public D | 677.8 | 836.9 | 1,031.6 | 813.3 | 1,412.1 | 1,841.9 | 1,791.6 |
| | Private D | 698.2 | 862.0 | 1,062.6 | 837.7 | 1,454.5 | 1,897.2 | 1,845.4 |
| **Region 4** | Public A | 1,332.0 | 1,818.8 | 2,140.4 | 1,767.4 | 3,105.2 | 4,003.0 | 3,758.3 |
| | Private A | 1,371.9 | 1,873.3 | 2,204.6 | 1,820.4 | 3,198.4 | 4,123.1 | 3,871.0 |
| | Public B | 1,030.9 | 1,272.8 | 1,326.1 | 1,236.9 | 1,802.0 | 2,801.4 | 2,726.1 |
| | Private B | 1,061.8 | 1,311.0 | 1,365.9 | 1,274.0 | 1,856.0 | 2,885.4 | 2,807.9 |
| | Public C | 827.9 | 1,022.2 | 1,203.7 | 993.3 | 1,637.8 | 2,175.6 | 2,342.7 |
| | Private C | 687.9 | 849.3 | 1,046.9 | 825.3 | 1,433.1 | 2,103.1 | 1,818.2 |
| | Public D | 687.9 | 849.3 | 1,046.9 | 825.3 | 1,433.1 | 1,869.2 | 1,818.2 |
| | Private D | 708.5 | 874.8 | 1,078.3 | 850.1 | 1,476.1 | 1,925.3 | 1,872.7 |
| **Region 5** | Public A | 1,374.8 | 1,877.2 | 2,209.2 | 1,824.2 | 3,205.0 | 4,131.7 | 3,879.0 |
| | Private A | 1,416.0 | 1,933.5 | 2,275.5 | 1,878.9 | 3,301.1 | 4,255.6 | 3,995.4 |
| | Public B | 1,064.0 | 1,313.7 | 1,368.7 | 1,276.6 | 1,859.9 | 2,891.4 | 2,813.7 |
| | Private B | 1,095.9 | 1,353.1 | 1,409.8 | 1,314.9 | 1,915.7 | 2,978.1 | 2,898.1 |
| | Public C | 854.5 | 1,055.0 | 1,242.4 | 1,025.2 | 1,690.4 | 2,245.5 | 2,418.0 |
| Regional | Hospital | Sepsis with GTI | Sepsis with NMI | Sepsis with UTI | UFI sepsis | Sepsis with LRTI | Sepsis with CVI | Sepsis with WI* |
| | Private C | 880.1 | 1,086.7 | 1,279.6 | 1,056.0 | 1,741.1 | 2,312.8 | 2,490.5 |
| | Public D | 710.0 | 876.6 | 1,080.6 | 851.8 | 1,479.1 | 1,929.3 | 1,876.6 |
| | Private D | 731.3 | 902.9 | 1,113.0 | 877.4 | 1,523.5 | 1,987.2 | 1,932.9 |

*Including surgical site infections.
*Note:* The colors indicate the difference between the PNP for sepsis with focal infections with the rates specified for the INA-CBGs (the green indicates a group of low PNPs with a small difference (< US$500), the blue indicates a group of middle PNPs with a medium difference (US$500–1,000), and the red indicates a group of high PNPs with a major difference (> US$1,000)). The comparison between PNP and INA-CBG rates is provided in Supplement 3.
**Abbreviations:** CVI, cardiovascular infections; GTI, gastrointestinal tract infection; ICU, intensive care unit; INA-CBGs, Indonesia Case Base Groups; LRTI, lower-respiratory tract infection; NMI, neuromuscular infection; PNP, proposed national price; UFI, unidentified focal infection; UTI, urinary tract infection; WI, wound infection.

and under-reported focal infections. However, the study was conducted with a big sample size to provide epidemiological and health economic findings that are needed by the Indonesian government for improving the new health insurance system with a resource-limited setting. Last, it did not consider following hospital discharge, particularly for ICU patients. Evidently, the higher mortality rate among sepsis patients after being discharged was a late-onset outcome of their ICU stays (Aguiar-Ricardo et al. 2019; Biason et al. 2019; Freitas et al. 2019).

## Conclusions

It is essential to consider mortality and focal infections in an assessment of the burden of sepsis. Each underlying focal infection determines the particular course of sepsis. In a resource-limited context such as that of Indonesia, where a new UHC system has been introduced, the adequate provision of healthcare services requires a reevaluation and recalculation of the price for sepsis. Furthermore, in context, sepsis cases with multifocal infections and LRTIs should be categorized as high-burden sepsis cases, reflecting the most obvious examples requiring adjustments to the national price for private and public healthcare services reimbursement.

## Contributions

AKRP, NM, GA, RRW and MJP initially contributed to developing the concept and the design of the work. AKRP, NM, GA, SHW, UH, HH, and CWN provided patients, collected and confirmed the clinical data. AKRP, NM, GA, RRW, JvdS, and MJP conducted data

analyses and synthesis. All authors wrote and revised the work and approved the final draft before submission.

## Ethical approval

The study was approved by the ethical committee of Dr. Soetomo General Academic Hospital, Surabaya (No. 418/Panke. KKE/VII/2017), Airlangga University Hospital (No. 114/KEH/2017), and the National Center of Infectious Diseases at Prof. Dr. Sulanti Saroso Hospital, Jakarta (No. 02/xxxviii.10/5/2018). The study met the Indonesian governmental requirements on conducting research and the ethical principles for medical research involving human subjects under the Helsinki Declaration (World Medical Association 2013). All data was deidentified to guarantee patient anonymity.

## Conflict of interest

MJP received grants and honoraria from various pharmaceutical companies, none of which are related to this study. The other authors declare no conflict of interest.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2020.04.075.

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